backbone and a functional group capable of attaching to the phosphate group of the phospholipid anchor.

53. The composition of claim 25, wherein the liposome comprises a bioactive agent.--

REMARKS

In the July 6, 2000 Office Action, the Examiner rejected claims 1-44 under 35 U.S.C. §112 first paragraph stating that "specification does not enable any person skilled in the art to which it pertains, or with which is nearly connected, to use the invention commensurate in scope with the claims." The Examiner suggests that the "claims must be limited to liposomes made with specific phospholipids and the drop in blood pressure as the adverse reaction and indomethacin as the compound which is able to correct this adverse reaction."

First, with respect to claims 1-17, which all depend upon claim 1, it is indicated that the adverse reaction sought to be overcome is a drop in blood pressure, and characteristics of the specific phospholipids to which the invention may apply are recited. The only element of claims 1-17 which does not comply with the Examiner's suggestion is that claim 1 applies to a broader range of anti-inflammatory agents then simply indomethacin. Applicants respectfully submit that the term anti-inflammatory agent is well known within the art and persons of skill in the art will readily recognize anti-inflammatory agents, both steroidal and non-steroidal. Furthermore, the specification is not limited to indomethacin but states that the anti-inflammatory agents used in the invention may be steroidal or non-steroidal. (See page 12, lines 16-19). The Examiner has given no reason why the claim should be more limited than the broad disclosure presented in the specification. In particular, the Examiner has not indicated that other anti-inflammatory agents would not exhibit the same effects as indomethacin. Indomethacin is simply the preferred anti-inflammatory agent of the invention. The invention is broadly enabled with respect to both steroidal and non-steroidal anti-inflammatory agents, and Applicant is entitled to this broad scope of protection.

With respect to "adverse reactions", the Examiner seems to be misapplying the concept of enablement under the patent laws. The adverse reactions resulting from the administration of liposome compositions to animals are clearly listed in the specification at page 4, lines 37-47. The

specification neither states nor requires that the administration of liposomes which cause the adverse effect contain any other bioactive agent, although, of course, the incorporation of bioactive agents is included within the scope of the specification.

The Examiner also states that Applicants have not presented a rationale showing the capability of indomethacin to correct all adverse reactions. This is not required. Applicants have generally enabled, through the use of a specific example, the scope of the claims by showing that a particular anti-inflammatory agent has the capability of correcting a particular adverse reaction. In the absence of some showing by the Examiner that either (a) not all anti-inflammatory agents have the capability of correcting the particular adverse reaction, i.e. a blood pressure drop, or (b) that anti-inflammatory agents do not suppress the other adverse reactions described in the specification, the specification is sufficiently enabled to allow a person skilled in the art to practice the claimed invention. MPEP 2164.02 ("Applicant need not describe all actual embodiments."); MPEP 2164.07 ("the Examiner has the initial burden of challenging an asserted utility. Only after the Examiner has provided evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the Applicant."); In re Marzocchi 169 USPQ 367, 369 (CCPA 1971) ("a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of §112 *unless* there is reason to doubt the objective truth of the statement contained therein.") (Emphasis in original).

The Examiner has presented no evidence that the claims are not entitled to the full scope in consideration of the disclosure. Specifically, "adverse reactions" are fully described in the specification as noted above, "anti-inflammatory agents" is a term readily recognized by a person of ordinary skill in the art, and the liposomes of the invention are fully described throughout the specification, and in particular, at page 4, line 48, through page 7, line 13.

Accordingly, because the Examiner has not met the burden of showing a lack of enablement, the claims are fully enabled by the disclosure, and applicants respectfully request that the rejection of claims 1-44 based on non-enablement be withdrawn.

In the Office Action, the Examiner has rejected claims 18-24 under 35 U.S.C §112 second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject

matter which Applicant regards as the invention. The Examiner asks "what is being conveyed through claim 18? What is the animal treated for? What is the distinction between "bioactive agent" and "anti-inflammatory agent"?" Applicants respectfully submit that claims 18-24 as amended, clearly answer the questions raised by the Examiner.

In particular, the liposome used in the invention comprises a "bioactive agent". Typical bioactive agents are listed on page 2, lines 53-65 and again at page 7, lines 14-43. Applicants respectfully submit that a person of ordinary skill in the art would know what particular treatments the various bioactive agents listed in the specification are useful for. In particular, those bioactive agents listed in the specification are those which would be administered in a liposome. Although anti-inflammatory agents are identified as possible bioactive compounds, there is a general distinction made between the bioactive agent and anti-inflammatory compound throughout the specification and particularly at page 12, lines 1-23. For example, page 7, lines 14 and 15 states that "the liposome used in the method of this invention comprises a bioactive agent". Page 12, lines 3-6 states that the method of the invention comprises administering and "an anti-inflammatory agent *and* a liposome composition" (emphasis added) and that the liposome composition comprises a bioactive agent. Page 12, line 6. Thus, a person skilled in the art would know what the animal is being treated for, and, in contrast to the Examiner's assertion, the specification distinguishes the bioactive agent, which is contained in the liposome, and anti-inflammatory agent, which is not.

The Examiner also states that "if the liposome composition induces an adverse reaction, it is unclear why it is administered and how this adverse reaction is reduced." Applicants submit that a person skilled in the art reading the disclosure would know that the adverse reactions, such as those listed on page 4, although resulting from administration of the liposome composition, are not the desired results of administration. In other words, although the liposome composition is administered for a beneficial effect, adverse effects, which are essentially side-effects, also occur. It is common knowledge that many compositions, such as drugs, administered for their beneficial effects also result in side effects. It is the reduction of these adverse side-effects that the present invention addresses. Thus, it would be clear to a person of ordinary skill in the art why the liposome composition is administered. The disclosure provides an adequate description as to what adverse reactions are caused by liposomes.

Claims 36-38 and claim 41 have been amended to depend on claim 33, thus providing the

proper antecedent basis for the terms "surface of modified agent" in claims 36-38, and the term "anchor" in claim 41. Accordingly, Applicants respectfully request that these rejections of the claims be withdrawn.

The Examiner also rejected claims 18, 21, 23, 25 and 27 under 35 U.S.C. §102(b) as being anticipated by Mezei and claims 18, 20, 22, 25, 26 and 28 under 35 U.S.C. §102(b) as being anticipated by JP60152414 or JP63264517. Claim 25 has been amended to more clearly point out that the composition comprises a liposome in combinations with a non-encapsulated anti-inflammatory agent. Thus, claim 25 and dependent claims 26, 27 and 28 are clearly distinguished from Mezei and the Japanese references which teach a liposome encapsulated anti-inflammatory agent. Applicants thus submit that the composition claims, as amended, are not anticipated by Mezei or the Japanese references and Applicants respectfully request that this rejection be withdrawn.

With respect to the method claims, i.e. claims 18, 23 and claims dependent thereon, Applicants respectfully traverse the Examiner's rejection. Even if Mezei and the Japanese references disclose the composition of the present invention (which they do not), the method of the present invention is not disclosed. Specifically, there is no teaching in Mezei or the Japanese references of a method of treating an animal comprising administering a liposome composition which causes an adverse affect in the absence of an anti-inflammatory agent and reducing that adverse reaction by administering an anti-inflammatory agent to the animal. The only thing disclosed in any of those references is the administration of an anti-inflammatory agent in a liposome vehicle in order to deliver the anti-inflammatory agent to the target. Thus, the administration of an anti-inflammatory agent to specifically reduce an adverse physiological reaction caused by the administration of the liposome composition is not anticipated by any of the references cited by the Examiner. The reduction of an adverse physical reaction is a necessary element of the claims and, because this element is missing from the references, they can not anticipate the claims. Accordingly, Applicants respectfully request that the rejections of claims 18-23 in view of Mezei or the Japanese references under 35 U.S.C. 102(b) be withdrawn.

The Examiner has also rejected claims 18, 19, 21, 23-25, 27, 33-36 and 43-44 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,023,087 to Yau-Young. The Examiner asserts that Yau-Young discloses a method of treating an animal with liposomes containing anti-

inflammatory agent and empty liposomes.

Yau-Young is primarily concerned with controlling the release rate of bioactive agents from liposomes by administering the drug-containing liposomes in combination with the empty liposomes. (col. 5, line 65 to col. 6, line 5). Thus, as with Mezei and the Japanese references, Yau-Young is concerned with delivering a drug entrapped within a liposome rather than in counteracting the adverse reactions caused by liposome administration as required in the method claims of the present invention. Accordingly, for the same reasons as for the Mezei and Japanese references, Yau-Young cannot anticipate the method claims, i.e. claims 18-24 of the present application.

With respect to the composition claims, Applicants note that, as with Mezei and the Japanese references above, the liposomes of Yau-Young contain an anti-inflammatory agent whereas, in the presently claimed composition, the anti-inflammatory agent is non-encapsulated. Thus, Applicants respectfully submit that Yau-Young cannot anticipate the claims of the present invention. Accordingly, Applicants respectfully request that the Examiner withdrawal the rejection under 35 U.S.C. 102(b) in view of Yau-Young.

The Examiner also rejected claims 33-44 under 35 U.S.C. 103(a) as being unpatentable over JP63964517 or Yau-Young, individually or in combination, in further view of Park; or Park in view of either Yau-Young or the Japanese references. The Examiner asserts that the Japanese references and Yau-Young lack the teaching of the modification of the surface of liposomes using carboxylic acids. The Examiner further asserts that Park teaches that liposomes modified with carboxylic acids prolong the circulation of liposomes and that Park's teaching are generic with respect to the active agent incorporated.

Although it may be correct to modify the teachings of the Japanese references or Yau-Young in view of Park to include carboxylic acids in the liposome structure, Applicants note that claim 33 teaches a composition comprising a liposome in combination with an anti-inflammatory agent. Neither the Japanese reference, Yau-Young, or Park, either taken individually or in combination, disclose this particular composition. As described above, all of the references cited by the Examiner concern the delivery of either an anti-inflammatory agent or some other bioactive agent such as a contrast agent, but none of the references relied upon by the Examiner disclose a liposome and a non-encapsulated anti-inflammatory agent. Without reading the specification of the present application, a person of ordinary skill in the art would have no reason to combine a

liposome and an anti-inflammatory agent.

Finally, the Examiner rejected claims 29-32 under 35 U.S.C. §103(a) as being unpatentable over JP 63264517 or Yau-Young cited above by themselves or in further view of Park or Park in view of Yau-Young and the Japanese reference in further combination with Cheng. The Examiner relies on the disclosure of Cheng to provide a teaching for the use of liposome for encapsulating contrast agents. Applicants respectfully submit that, similar to the other references, Cheng does not disclose the use of a contrast agent in conjunction with anti-inflammatory agents. At best, a person of ordinary skill in the art reading these references would insert the contrast agent of Cheng into one of the liposomes described in the other references in place of an anti-inflammatory agent and not in conjunction with an anti-inflammatory agent as required by claim 29 and its dependent claims. Accordingly, the invention of claims 29-32 would not have obvious to a person of ordinary skill in the art.

Applicants respectfully submit that the present claims are in condition for allowance and respectfully request that claims 1-53 be allowed and the application passed to issue. Should any questions of patentability remain, the Examiner is invited to contact undersigned counsel to resolve such questions.

Respectfully submitted,

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